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Physical and Respiratory Training in Patients with Myasthenia Gravis: A Systematic Review with Meta-Analysis

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Abstract:

Introduction: Myasthenia gravis is a chronic autoimmune disorder that affects the neuromuscular junction, leading to impaired muscle function. This systematic review aimed to evaluate the current scientific evidence on the effects of training programs on symptom severity, performance in activities of daily living, quality of life, physical fitness, and respiratory function in individuals with myasthenia gravis.

Methods: A systematic review and meta-analysis were conducted following the PRISMA guidelines. Searches were performed in PubMed, Scopus, Web of Science, and CINAHL Complete databases. Outcomes of interest included symptom severity scores, quality of life, activities of daily living performance, physical fitness, and respiratory parameters.

Results: A total of 1564 records were identified. After removing duplicates and screening titles, abstracts, and full texts, 20 studies were included in the qualitative synthesis, with 10 of them contributing to quantitative meta-analyses. Training interventions were associated with reductions in symptoms, as well as improvements in quality of life and performance in activities of daily living. Additionally, enhancements were observed in muscle strength, distance covered, and respiratory parameters.

Conclusion: Physical activity and respiratory training may offer multiple benefits for patients with myasthenia gravis. Nevertheless, individualized

exercise programs are essential to ensure safety and optimize adherence among this population.

Keywords: Myasthenia gravis; Physical activity; Respiratory training; Systematic review; Meta-analysis.

1. Introduction

Autoimmune diseases result from aberrant immune responses against self-tissues [1]. Their burden has risen significantly: recent estimates indicate a 12.5% prevalence, and incidence rate of 19.9% [2]. In the United States, prevalence increased from 11% (22.3 million individuals) in the 1990s to 16.1% (41.5 million) in 2011-2012 [3]. Within this spectrum, neuromuscular autoimmune disorders are individually rare but collectively substantial [4]. In Europe, prevalence of neuromuscular diseases is 24.3 cases per 100,000 inhabitants, corresponding to 182,000 individuals [5]. One notable example of such disorders is myasthenia gravis (MG), which currently impacts a significant number of patients worldwide [6].

MG is an autoimmune disorder caused by autoantibodies targeting acetylcholine receptors at the neuromuscular junction. This immune-mediated interference disrupts the transmission of nerve impulses, impairing normal muscle contraction [7]. The global prevalence of MG is currently estimated at 12.4 cases per 100,000 inhabitants, with a higher incidence observed among women aged 20-30 years and a second peak in individuals over 65 years of age. However, recent studies have reported a rising

prevalence among men over the age of 50 [8]. Globally, the incidence of MG ranges from 1.7 to 30 new cases per million inhabitants per year [8]. In Spain, the estimated prevalence is 260 cases per 1,000,000 inhabitants, with an annual incidence of 15.4 new cases per 100,000 inhabitants [7].

This continuous rise in MG cases may have a substantial economic impact on national health care systems, affecting both population health and the system's capacity to respond [9]. In Spain, the average annual cost of treating a patient with MG is estimated at 5,955€ [10]. In other European countries, such as Italy, the total direct healthcare cost per MG patient is approximately 3,771€—four times higher than that on the general population (869€), and up to 7,827€ for patients experiencing disease exacerbations [9]. Moreover, studies analyzing the European population have reported that the average annual indirect costs associated with MG range from 2,790 to 10,321€, often exceeding direct medical costs. These indirect costs are primarily attributed to early retirement, sick leave, temporary or permanent disability, and informal caregiving [11,12]. The level of dependency associated with MG is also significant, frequently requiring the support of caregivers, adapted housing and transportation, and technical or orthopedic aids. Therefore, promoting the health and autonomy of individuals with MG is of critical importance [13].

Regarding the treatment of MG, several high-cost therapeutic options are currently in use. These include acetylcholinesterase inhibitors, immunosuppressive agents (such as corticosteroids, azathioprine, cyclosporine, and tacrolimus), biological therapies (e.g., efgartigimod), intravenous immunoglobulins, therapeutic plasma exchange (plasmapheresis) and thymectomy [14,15]. However, it is important to note that there is no definitive cure for MG. Current treatment strategies are

primarily aimed at achieving and maintaining clinical remission [14,15]. In this context, non-pharmacological interventions, such as physical activity (PA), may play a valuable role in MG because it can help alleviate these symptoms of the disease [16], promote adequate muscle function, and improve key health outcomes, including quality of life and independence in basic activities of daily living (ADL) [17,18]. In MG, individualized and structured exercise programs tailored to each patient's capacities may help enhance muscle strength in both affected and unaffected muscle groups [18,19]. Additionally, resistance training and respiratory muscle exercise have shown promise in improving physical performance and aerobic capacity in individuals with MG [18,19].

Effective management of PA in patients with MG requires a multidisciplinary approach, involving collaboration among nurses, physiotherapists, physicians, and exercise professionals with the aim of delivering comprehensive care that supports optimal disease management and improves patient outcomes [20,21]. Exploring the relationship between PA and MG is particularly important, as some authors have reported that physical exertion may trigger a recurrence of MG symptoms [22]. Conversely, other studies suggest that PA is well tolerated by individuals with MG and may contribute to symptom control and overall well-being [23].

Given the ongoing debate regarding the effects of PA on MG, further investigation is warranted to critically assess this relationship. Such research could serve as the foundation for developing new clinical guidelines and recommendations aimed at improving the health and quality of life of individuals with MG. These guidelines would be valuable not only for patients, but also for healthcare professionals involved in their care. Therefore, the objective of this review is to analyze the available scientific evidence on the

impact of PA on symptoms, performance in ADL, quality of life, physical fitness, and respiratory function in patients with mild to moderate MG.

2. Methodology

2.1. Study design and information sources

To address the proposed objective, a systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. This review was registered in the PROSPERO registry with registration number CRD420251036614.

Bibliographic research was performed in the Pubmed, Scopus, Web of Science and CINAHL Complete databases.

2.2. Search strategy

Database searches were designed to answer the research question based on the population, intervention, control and outcome (PICO) framework (Table 1).

Table 1. PICO question

Population	**Intervention**	**Control**	**Outcome**
Individuals with mild to	Aerobic physical exercise, respiratory muscle	Sedentary MG patients, control groups or habitual	Symptoms, quality of life, performance in ADL, physical

moderate MG	training, or assessment of habitual PA	PA (not supervised by investigators)	condition and respiratory function

Therefore, the research question weas: What is the impact of PA on symptoms, quality of life, ADL performance, physical condition and respiratory function in patients with MG?

Searches were conducted during April and May 2025. For each database, MeSH terms and Boolean operators were applied as specified in the search strings (Table 2).

Table 2. Detailed searches

Database	**Search string**	**Filters**

Pubmed	(Myasthenia Gravis) AND (Exercise OR Exercise Therapy OR Training OR Health Strategies OR Resistance Training OR Muscle Strength) NOT (Animals) NOT (Immunoglobulin) NOT (laboratory) NOT (Efgartigimod) NOT (Antibodies)	English or Spanish
Web of Science	TS = ((Myasthenia Gravis) AND (Exercise OR Exercise Therapy OR Training OR Health Strategies OR Resistance Training OR Muscle Strength) NOT (Animals) NOT (Immunoglobulin) NOT (laboratory) NOT (Efgartigimod) NOT (Antibodies))	English or Spanish
Scopus	TITLE-ABS ("Myasthenia Gravis") AND TITLE-ABS (exercise) OR TITLE-ABS ("Exercise therapy") OR TITLE-ABS (training) OR TITLE-ABS ("health strategies") OR TITLE-ABS ("resistance training ") OR TITLE-ABS (" muscle strengths ") AND NOT TITLE-ABS (animals) AND NOT TITLE-ABS (immunoglobulin) AND NOT TITLE-ABS (laboratory) AND NOT TITLE-ABS (efgartigimod) AND NOT TITLE-ABS (antibodies)	English or Spanish
CINAHL Complete	(Myasthenia Gravis) AND (Exercise OR Exercise Therapy OR Training OR Health Strategies OR Resistance Training OR Muscle Strength) NOT (Animals) NOT (Immunoglobulin) NOT (laboratory) NOT (Efgartigimod) NOT (Antibodies)	English or Spanish

2.3. Inclusion and exclusion criteria

To determine the suitability of studies for inclusion in this review, the following inclusion criteria were applied: (1) studies employing a randomized clinical trial (RCT) design, quasi-experimental, longitudinal observational (prospective or retrospective), or cross-sectional methodologies; (2) studies with samples composed exclusively of MG patients; (3) studies that analyzed the impact of PA on the clinical status of MG; (4) articles published in Spanish or English.

Conversely, articles with the following characteristics were excluded: (1) studies focusing on neurological disorders other than MG; (2) studies evaluating pharmacological interventions without considering PA; (3) animal studies; (4) studies involving pediatric samples; (5) pilot studies (due to insufficient outcome reporting), grey literature (due to potential limitations in methodological rigor), narrative or systematic reviews, meta-analyses, case reports, and case series.

2.4. Selection process

The selection of studies was conducted independently by two reviewers (GGV and VSF) based on the predefined inclusion and exclusion criteria. Mendeley reference manager software was used to organize citations and remove duplicates. After duplicate removal, titles and abstracts were screened to identify studies eligible for full-text review. Subsequently, full-text articles were assessed to determine their inclusion in the qualitative synthesis. Any discrepancies during the selection process were resolved through discussion between the two reviewers. If consensus could not be reached, a third reviewer (JALA) was consulted to make the final decision.

2.5. Assessment of methodological quality

To evaluate the risk of bias in the selected studies, the following tools were used bases on study design: the risk of bias 2 (RoB-2) tool [25] for randomized controlled trials (RCT), the risk of bias in nonrandomized studies of exposures (ROBINS-E) [26] for observational studies, and risk of bias in nonrandomized studies of interventions (ROBINS-I) [27] for non-randomized and quasi-experimental designs.

RoB-2 tool [25] covers five domains (randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result), ROBINS-E [26] includes seven domains (confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result), and ROBINS-I [27] also includes seven domains tailored to exposures (confounding, exposure measurement, selection of participants, post-exposure interventions, missing data, outcome measurement, and selection of the reported result).

All tools were applied via their signaling questions (Yes, Probably yes, No, Probably no, No information; Not applicable when relevant). Overall study-level judgments followed each tool’s decision algorithm. Specifically: RoB-2—Low if all domains were low; Some concerns if at least one domain raised some concerns, and none were high; High if at least one domain was high. ROBINS-E—Low, Some concerns, High, or Very high, likewise determined by the highest-risk domain. ROBINS-I—Low, Moderate, Serious, or Critical with the overall rating determined by the worst domain.

In all cases, the risk of bias was independently assessed by two authors (VSF and GGV). Inter-reviewer reliability was high. Any discrepancies were resolved by consulting JALA and JMCT until a consensus was reached.

2.6. Data extraction

Data extraction was performed by VSF and GGV. The following information was collected from each included study: (1) authors, year and country; (2) study design; (3) characteristics of the population; (4) study intervention; (5) main results; and (6) conclusions.

The effectiveness of PA was evaluated based on its impact on symptoms, quality of life, and respiratory function in patients with MG. For symptom assessment, the following validated clinical scales were used: the quantitative myasthenia gravis (QMG) score, myasthenia gravis composite (MGC) score, and Besinger score. Quality of life was assessed using the Myasthenia Gravis Quality of Life 15-item (MG-QOL15) score. Regarding respiratory function, the following parameters were considered: forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and maximum inspiratory pressure (PImax).

Additionally, secondary outcomes included improvements in muscle strength, fatigue, aerobic endurance, and performance in ADL.

2.7. Data analysis

A qualitative synthesis of the selected studies was conducted to analyze the clinical status of patients with MG who participated in PA interventions across various studies. Statistical analyses were conducted using Review Manager v5.4.

In addition, a quantitative synthesis was performed using the reported variables. For this purpose, means and standard deviations of scores related to both primary and secondary outcomes were extracted and included in random-effect meta-analyses, using the inverse variance method. When studies reported medians and interquartile ranges, these values were converted to mean and standard deviation following the methodology proposed by Luo D et al.[28]. Additionally, to assess publication bias, funnel plots were visually inspected for each meta-analysis conducted.

Heterogeneity among outcome variables was evaluated using I^2 statistic, with values 0-40% (might not be important), 30-60% (may represent moderate heterogeneity), 50-90% (may represent substantial heterogeneity), and 75-100% (considerable heterogeneity) based on the Cochrane Handbook [29]. Statistical significance was defined as p values <0.05 for two-tailed hypothesis contrasts.

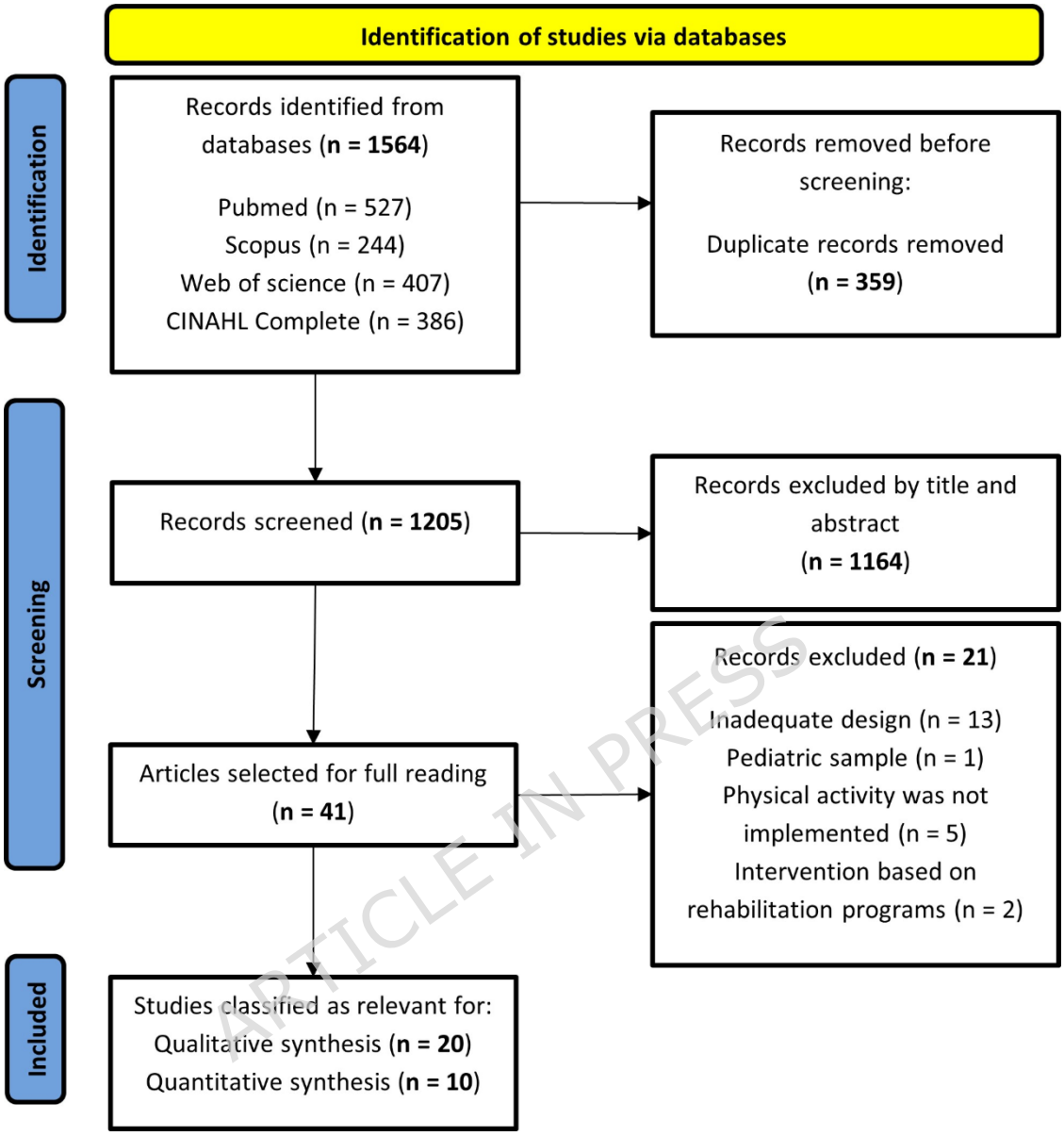
3. Results

3.1. Study selection

Following the comprehensive search strategy applied across all databases, a total of 1,564 records were initially identified. After removing 359 duplicates using the Mendeley reference manager, 1,205 unique records remained. Upon screening titles and abstracts, 1,164 studies were excluded for not meeting the inclusion criteria. Consequently, 41 full-text articles were assessed for eligibility.

Of these, 20 studies [30–49] were included in the qualitative synthesis, while 10 studies [30,34,38–40,42–44,46,47] were eligible for inclusion in the quantitative meta-analyses. The detailed study selection process is illustrated in the PRISMA flow diagram (Figure 1).

Figure 1. PRISMA flowchart of the selection of results



3.2. Characteristics of the included studies

The review included a total of 20 studies [30–49] comprising seven RCT [35–38,40,48,49], five non-randomized trials [39,44–47], and eight observational studies [30–34,41–43]. Collectively, these studies involved a total sample of 1,366 adult patients diagnosed with MG, classified according to the Myasthenia Gravis Foundation of America (MGFA) as class I-III (mild to

moderate severity). Among the participants, 592 (43.4%) were male and 774 (56.6%) were female, with ages ranging from 16 to 75 years.

Of the included studies, fourteen evaluated the effects of aerobic PA [30–42,49], while six focused on respiratory muscle training in MG patients [43–48]. The types of PA interventions varied and included walking [30,49], stationary cycling using an ergometer [35–40,42], strength training [39], and respiratory muscle training [43–48]. However, five studies [31–34,41] did not specify the type of PA performed, limiting the ability to categorize the intervention precisely. As a result, the interventions applied across the studies were heterogeneous in nature [30–49]. Detailed information on the characteristics of the included studies is presented in Table 3.

Table 3. Results table

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Tripathi G, et al.[30] 2023 India	Prospective observational study	27 participants (15 with MG, 12 healthy controls)	Daily 30-minute walking sessions for 3 months	In MG group, there is a decrease in MG-QOL 15 and MG-ADL scores ($p < 0.001$). The steps and distance of the 6MWT were increased (p values 0.007 and 0.03, respectively)	Aerobic PA improves quality of life, ADL performance, and mobility in MG patients	Some concerns
Thomsen J, et al.[31] 2022 Denmark	Longitudinal cohort study	105 participants (70 MG patients, 35 healthy controls)	PA and mobility assessed via Physical Activity Scale and 400MWT	In MG group, there was a 10.8% increase in shoulder strength ($p < 0.001$); 400MWT correlated with QMG ($R=0.43$, $p < 0.05$) and MG-QOL15 ($R=0.31$, $p < 0.05$); no significant correlation with MGC ($R=0.05$)	PA is associated with increased strength, symptom improvement, and better quality of life in MG patients	Low
Salci Y, et al.[32] 2019	Observational cross-	31 MG patients	Functional capacity assessed via 6MWT and 2MWT	Correlation 2MWT/MG-QOL15 -0.45 ($p = 0.01$); 2MWT/QMG -0.53 ($p = 0.002$);	2MWT and 6MWT are well tolerated. Higher performance is associated with fewer	Low

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Turkey	sectional study			Correlation 6MWT/MG-QOL15 -0.47 (p =0.007); 6MWT/QMG -0.57 (p <0.001)	symptoms and better quality of life	
Birnbaum S, et al.[33] 2021 France	Prospective observational study	99 female participants (33 MG; 66 controls)	Assessment of PA and sedentary behavior patterns	MG group showed significantly lower PA levels than controls (p<0.001); PA correlated with 6MWT (R=0.38, p=0.03); no correlation with quality of life or symptom severity	MG patients are less active than healthy controls. PA is associated with better performance but not with quality of life or MG symptoms	Some concerns
Andersen L, et al.[34] 2021 Denmark	Cross-sectional study	779 MG subjects	Online questionnaire assessing PA, symptoms, fatigue, and quality of life	53% of subjects reported low PA levels: lower PA associated with greater fatigue (MFI-20 14 vs. 11, p <0.01), more symptoms (MG-ADL 3 vs. 2, p <0.01), and lower quality of life (MG-QOL15 12 vs. 7, p<0.01)	PA is beneficial for reducing fatigue and symptoms, and improving quality of life in MG patients	Low
				Intervention group showed significantly higher muscle		

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Deliana T, et al.[35] 2025 Indonesia	RCT	20 MG patients (10 intervention, 10 control)	Aerobic exercise using ergometer. 3 sessions/week of 30 minutes for 8 weeks.	strength (71.7 ± 3.7 vs. 64.6 ± 3.2, p<0.001) and endurance (107.1 ± 7.6 vs. 83.2 ± 4.1, p<0.001) compared with control group	Aerobic exercise for 8 weeks significantly improves muscle strength and endurance in MG patients	Some concerns
Kartika L, et al.[36] 2024 Indonesia	RCT	17 MG patients (8 intervention, 9 control)	Aerobic exercise using ergometer. 3 sessions/week of 30 minutes for 8 weeks.	Intervention group showed increased walking speed (10MWT: 0.083 ± 0.015, p<0.001 vs. -0.081 ± 0.045, p=0.115); and improved fatigue (FSS: -0.017 ± 0.275, p=0.019 vs. -1.04 ± 0.306, p=0.054) compared to control group	Aerobic exercise for 8 weeks improves walking speed and reduces fatigue in MG patients.	Low
Putri T, et al.[37] 2024 Indonesia	RCT	20 MG patients (10 intervention, 10 control)	Aerobic exercise using ergometer. 3 sessions/week of 30	MGC score was significantly lower in intervention group (2.4 ± 1.84) compared to control group (6.0 ± 2.49), p=0.002	Low-intensity aerobic exercise reduces MG severity	Some concerns

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
			minutes for 8 weeks.			
Muslihah I, et al.[38] 2024 Indonesia	RCT	22 MG patients (11 intervention, 11 control)	Aerobic exercise using ergometer. 3 sessions/week of 30 minutes for 8 weeks.	MG-ADL score significantly lower in intervention group (5.73 ± 1.34) vs. control (7.55 ± 1.57), p=0.009	Low intensity aerobic exercise contributes to improving ADL performance in MG patients	Low
Rahbek M, et al.[39] 2017 Denmark	Quasi-experimental study	12 MG patients (6 resistance training, 6 aerobic training)	20 sessions over 8 weeks of progressive resistance (strength exercises) or aerobic training with ergometer	QMG score decreased from 5.5 to 4.5 in resistance group (p=0.5) and from 6.5 to 4.5 in aerobic group (p=0.65); no significant differences between groups.	Moderate- to high-intensity exercise is feasible and safe in MG patients	Moderate

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Birnbaum S, et al.[40] 2021 France	RCT	43 MG patients (23 intervention, 20 control)	Aerobic exercise using ergometer. 3 sessions/week of 30 minutes for 12 weeks.	No significant differences in MG-QOL15 score (p=0.72); aerobic capacity improved in intervention group compared to control group, p=0.01.	Aerobic training is well tolerated and improves aerobic capacity in MG patients	Some concerns
Alsop T, et al.[41] 2022 Australia	Cross-sectional study	85 MG patients	Self-administered questionnaire assessing PA, fatigue, and quality of life	62.4% of the sample was classified as physically active. Correlation R^2 PA/fatigue = 0.196 and PA/MG-QOL15 = 0.330, $p<0.05$	PA is associated with favorable health outcomes and well-being in MG patients	Low
Chang C, et al.[42] 2021 Taiwan	Prospective observational study	34 MG patients	Aerobic training with ergometer. 30-minute sessions for 24 weeks (weekly frequency self-selected)	QMG score decreased from 10.47 ± 4.78 to 9 ± 5.22 (p=0.024); MG-QOL15 decreased from 14.91 ± 11.29 to 11.41 ± 12.24 (p=0.085)	Aerobic PA is safe and beneficial for functional outcomes in MG patients	Low

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Misra U, et al.[49] 2021 India	RCT	38 MG patients (19 intervention, 19 control)	Aerobic training, 30-minute walking sessions every day for 3 months	Muscle strength increased in intervention group (68 ± 14 to 84 ± 10, p<0.001), and control group (60 ± 15 to 74 ± 20, p<0.001). 100% of intervention group improved quality of life by 50% vs 68.5% in control (p=0.02)	30-minutes daily walking improves quality of life and physical capacity in MG patients	Low
Hsu C, et al.[43] 2020 Taiwan	Prospective observational study	34 MG patients (18 intervention, 16 control)	Respiratory muscle training. 2 sets of 3 repetitions with training device for 12 weeks.	QMG score improved in intervention group from 9.5 to 7.5, p value = 0.02. FVC increased from 77.9 ± 12.6% to 83.8 ± 17.7%, p = 0.03. No significant changes in control group	Respiratory training improves lung function and overall condition in MG patients	Low
Weiner P, et al.[44] 1998	Non-randomized clinical trial	18 MG patients (10 intervention, 8 control)	Respiratory muscle training. 30-minute sessions, 6	Inspiratory pressure increased in both groups (56.6 ± 3.9 to 87.0 ± 5.8 cmH20, p <0.001 in	Respiratory muscle training may be a safe	Moderate

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Israel			times/week for 3 months.	intervention group; in control group increased from 28.9 ± 5.9 to 45.5 ± 6.7 cmH20, p <0.005)	and effective therapeutic option for MG patients.	
Rassler B, et al.[45] 2007 Germany,	Quasi-experimental study	10 patients with MG.	Respiratory muscle training. 30-minute sessions, 5 times/week for 4-6 weeks	Besinger score showed a non-significant change from 0.74 ± 0.10 pre-intervention to 0.66 ± 0.09 post-intervention. MVV pre-intervention increased non-significantly from 98.2 ± 9.1% to 108.5 ± 8.3% post-intervention.	Muscular resistance training is feasible for MG patients regardless of disease severity.	Low
				Intervention group showed a decrease in the Besinger score	An increase in expiratory resistance was observed.	

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Freitag S, et al.[46] 2018 Germany,	Non-randomized clinical trial	24 MG patients (18 intervention, 6 control)	Respiratory muscle training. 30-minute sessions, 5 times/week for 4 weeks	from 0.67 ± 0.09 to 0.22 ± 0.05, p <0.001. Non-significant changes in the control group. Time to exhaustion in intervention group of 26 ± 3.2 vs. 15.3 ± 4.6 minutes in control group, p value <0.001	In addition, respiratory resistance training contributes to improving MG symptoms.	Low
Rassler B, et al.[47] 2011 Germany,	Quasi-experimental study	10 MG patients.	Respiratory muscle training. 30-minute sessions for 4 weeks. Subsequently, 5 sessions every 2 weeks for 3 months	Besinger score showed a significant improvement (0.71 ± 0.12 pre-intervention vs. 0.56 ± 0.10 post-intervention, p=0.002). MVV pre-intervention of 110 ± 10.3 vs. 119 ± 11.1 L/min post-intervention, p=0.24	Respiratory resistance training may be performed safely in mild to moderate MG over several months.	Low
				Intervention group showed a significant increase in muscle		

Authors, year and country	Design	Participants	Intervention	Results	Conclusion	Risk of bias
Fregonezi G, et al.[48] 2005 Spain	RCT	27 patients with MG. 14 in the intervention group and 13 in the control group.	Respiratory muscle training. 45-minute sessions for 8 weeks.	strength (from 56 ± 22 to 71 ± 27 cmH_2O, p <0.001). Physical score of the HR-QOL short form-36 in intervention group went from 50 ± 43 to 71 ± 43, p <0.01. No significant changes in control group.	Respiratory exercise programs enhance respiratory muscle strength and quality of life in MG subjects.	Low

MG: Myasthenia Gravis. PA: Physical activity. MG-QOL 15: Myasthenia Gravis Quality of Life 15. This scale ranges from 0 to 60 points; lower scores indicate better quality of life. MG-ADL: Myasthenia Gravis Activity Daily Living. This scale ranges from 0 to 60 points; lower scores reflect better performance in basic daily activities. 6MWT: 6-Minute Walk Test; greater distance and step count indicate better physical condition. 2MWT: 2-Minute Walk Test; greater distance and step count indicate better physical fitness. ADL: Activity Daily Living. 400MWT: 400-meter Walk Test; longer completion times suggest poorer physical condition. QMG: Quantitative Myasthenia Gravis. Ranges from 0 to 39; lower scores indicate less severe disease. RCT: Randomized Clinical Trial. MFI-20: 20-item Multidimensional Fatigue Inventory. Scores range from 4 to 20; higher scores indicate greater fatigue. 10MWT: 10-meter Walk Test; greater distance and step count reflect better physical condition. FSS: Fatigue Severity Scale. Scores range from 9 to 63; higher scores indicate more severe fatigue. MGC: Myasthenia Gravis Composite. Ranges from 0 to 50; higher scores indicate more severe disease. FVC: Forced vital capacity. MVV: maximal voluntary ventilation. HR-QOL: health-related quality of life; Higher scores indicate better quality of life.

3.3. Characteristics of the selected studies

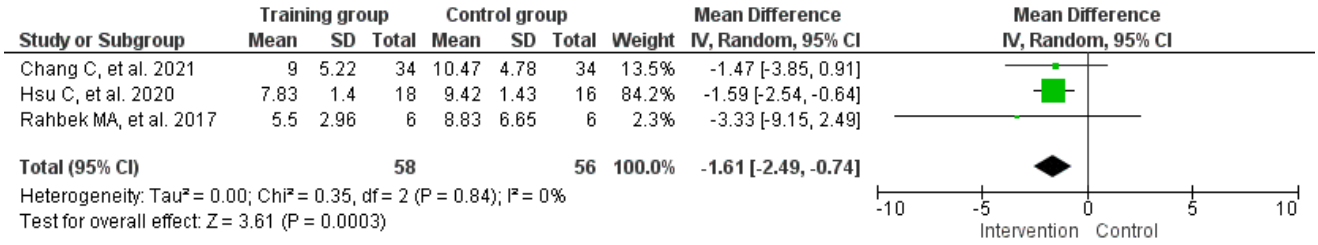
The risk of bias was evaluated for each type of study included. For RCTs[35–38,40,48], all studies were assessed as having a low risk of bias according to the RoB-2 tool (Figure S1). In contrast, when the ROBINS-E tool was applied, only two studies [30,33] were rated as having a moderate risk of bias, while the remaining studies [31,32,34,41–43] were classified as having a low risk of bias (Table S1). Finally, regarding the ROBINS-I tool, two studies [39,44] were rated as having moderate risk of bias, whereas the remaining studies [45–47] were considered to have a low risk of bias (Table S2).

3.4. MG symptoms

A total of seven studies [37,39,42,43,45–47] assessed symptom severity in patients with MG. One RCT [37] reported a significant reduction in the MGC score in the intervention group from 5.4 ± 2.32 to 2.4 ± 1.84 ($p < 0.001$). In contrast, the control group showed a non-significant increase in this score, from 5.4 ± 2.68 to 6 ± 2.49 points ($p = 0.193$).

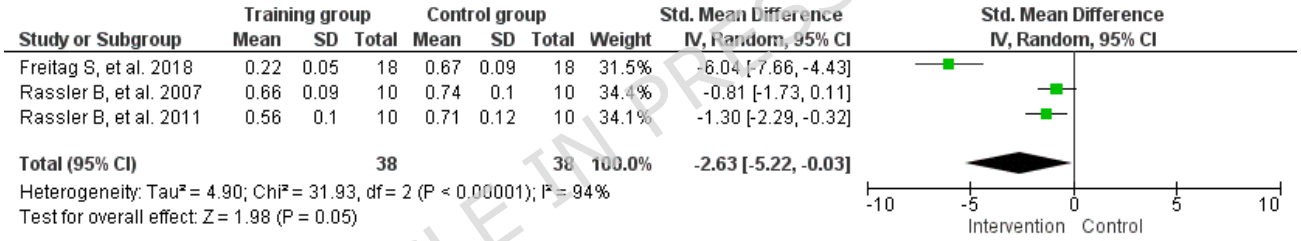
Another commonly used measure for evaluating MG symptoms is the QMG score. A random-effects meta-analysis was conducted using the mean and standard deviation values reported in three studies [39,42,43]. The analysis revealed a mean difference of -1.61 points [95%CI: -2.49,-0.74] in favor of the intervention, with heterogeneity $I^2 = 0\%$. The forest plot summarizing these results is presented in Figure 2, while the funnel plot illustrating potential publication bias is shown in Figure S2.

Figure 2. Forest plot of QMG score



Three studies[45–47] used the Besinger score to assess MG symptoms. A standardized mean difference of -2.63 points [95%CI: -5.22,-0.03] was observed in favor of the intervention, with heterogeneity I^2 = 94% (Figure 3). The corresponding funnel plot indicating publication bias is shown in Figure S3.

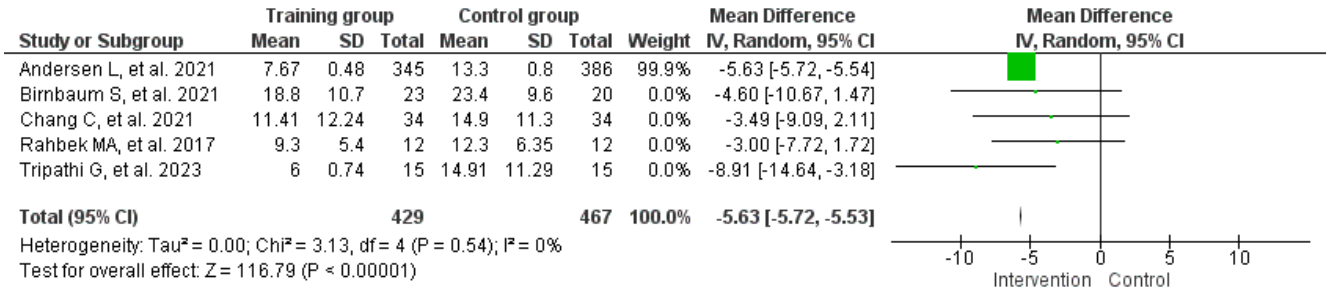
Figure 3. Forest plot of Besinger score



3.5. Quality of life

The quality of life of MG patients was evaluated in six studies[30,34,39,40,42,49]. All studies used the MG-QOL-15 tool. One RCT [49] reported that 100% of patients in the intervention group experienced a 50% improvement in quality of life, compared to 68.5% (13 subjects) in control group. In addition, for this outcome, a random-effects meta-analysis was performed using the means and standard deviations of the MG-QOL15 scores reported in several studies [30,34,39,40,42] (Figure 4). In this meta-analysis, a mean difference of -5.63 points [95%CI: -5.72,-5.53] was observed in favor of the intervention, with heterogeneity I^2 = 0%. Figure S4 shows the risk of publication bias for this meta-analysis.

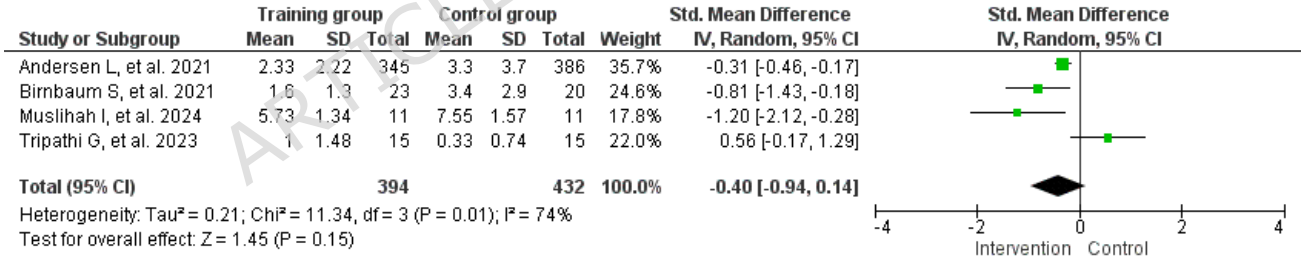
Figure 4. Forest plot for MG-QOL15 score



3.6. Performance for activities of daily living

The ability to perform ADL in patients with MG was analyzed in four studies using the MG-ADL score [30,34,38,40]. Figure 5 shows the random-effects meta-analysis, revealing a standardized mean difference of -0.40 points [95%CI: -0.94,0.14], with I^2 = 74%. Figure S5 shows the funnel plot of the risk of publication bias in this meta-analysis.

Figure 5. Forest plot for MG-ADL



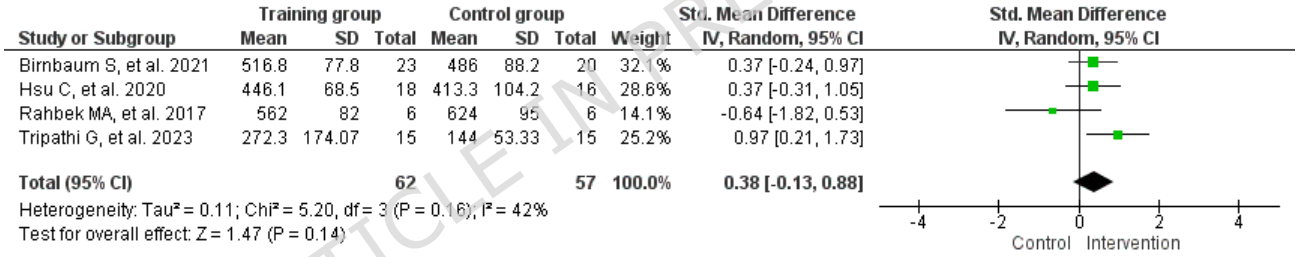
3.7. Muscle strength, endurance, and physical performance

In one RCT[35], significant improvements in muscle strength and endurance were reported in the PA group. Compared to control group, the mean activation of the vastus obliquus and lateralis muscles was significantly higher in the intervention group (71.7 ± 3.7 vs. 64.6 ± 3.2, p <0.001; and 70.9 ± 2.7 vs. 63.6 ± 3.3, p <0.001, respectively).

Notably, PA was associated with a 10.8% increase in muscle strength, and higher scores on the 400MWT were correlated with fewer MG symptoms [31]. Furthermore, performance on the 2MWT and 6MWT was correlated with an increase in quality of life[32].

A random-effects meta-analysis was performed, including studies that evaluated the effect of training on the distance covered in the 6MWT [30,39,40,43] (Figure 6). The analysis revealed an standardized mean difference of 0.38 meters [95%CI: -0.13,0.88] in favor of the intervention, with heterogeneity I^2 = 42%. Figure S6 shows the funnel plot of the risk of publication bias in relation to this meta-analysis.

Figure 6. Forest plot for 6MWT



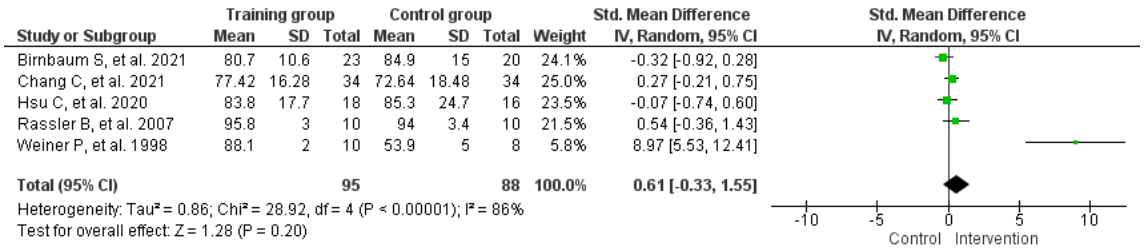
3.8. Respiratory function

Respiratory function of MG patients was evaluated in six studies [43–48]. Compared to control group, respiratory muscle training improved respiratory endurance (72.0 ± 4.2% vs. 43.4 ± 3.8%, p value <0.001)[44]. In addition, inspiratory muscle strength increased from 56 ± 22 to 71 ± 27 cmH2O (with p <0.001) [48]. Although maximum voluntary ventilation increased from 98.2 ± 9.1% to 108.5 ± 8.3%, this change did not reach statistical significance[48].

Another variable positively influenced by respiratory training was FVC. A random-effects meta-analysis (Figure 7), including five studies [40,42–44,47] demonstrated a standardized mean increase in FVC of 0.61 liters [95%CI: -

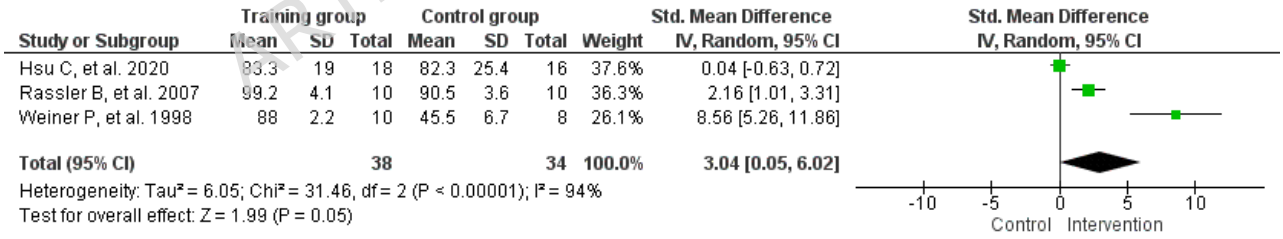
0.33,1.55], with heterogeneity of I^2=86%. The risk of publication bias is assessed through visual inspection of the funnel plot (Figure S7).

Figure 7. Forest plot for FVC



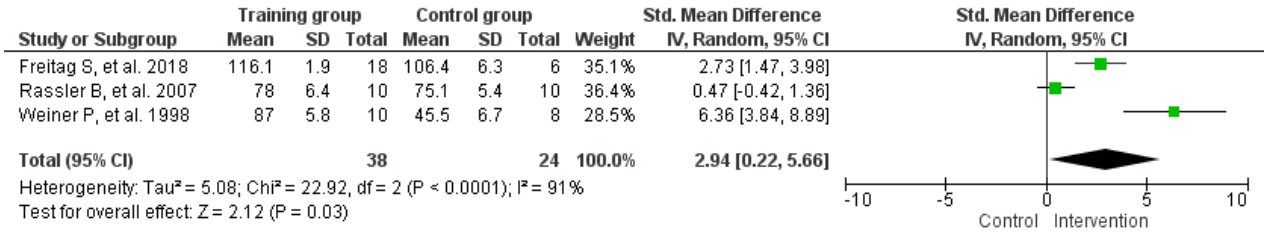
In addition, a random-effects meta-analysis (Figure 8) was performed to evaluate the impact of training on FEV1, using data from three studies [43,44,47] . The analysis revealed a standardized mean increase of 3.04 liters [95%CI: 0.05,6.02], with a level of heterogeneity I^2=94%. A visual inspection of the funnel plot (Figure S8) indicated the risk of publication bias in this meta-analysis.

Figure 8. Forest plot of FEV1



Finally, another random-effects meta-analysis was performed (Figure 9) to assess the effects of training on PImax based on three studies [44,46,47]. This meta-analysis showed a standardized mean difference of 2.94 cmH2O [95%CI: 0.22,5.66], with I^2 heterogeneity of 91%. The corresponding funnel plot (Figure S9) illustrates the risk of publication bias associated with this outcome for MG patients.

Figure 9. Forest plot of PImax



3.9. Compliance and safety of physical and respiratory training

Among the studies included in this review[30–49], seven reported participants dropouts during the training program[36,38–40,46,48,49]. In the study by Kartika L, et al.[36], three participants withdrew due to difficulties adhering to the training protocol. Muslihah I, et al.[38] reported dropouts for personal reasons, while Rahbek M et al.[39] noted two withdrawals due to lack of time to continue the intervention.

Additionally, five studies [39,40,46,48,49] reported dropouts related to MG-specific events or comorbidities. Four studies documented withdrawals due to myasthenic crises, one of which was attributed to poor adherence to pharmacological treatment [49]. Notably, in the study by Birnbaum S, et al.[40], hospitalizations occurred in the control group, which was instructed to maintain usual PA levels. Three studies [46,48,49] reported dropouts due to comorbid conditions, including kidney disease [49], cancer [48,49], pulmonary embolism, and surgical complications [46].

4. Discussion

The synthesis of the included studies[30–49] highlights the beneficial effects of PA and respiratory training on symptom severity, performance in ADL, quality of life, physical condition and respiratory function for patients with mild to moderate MG. These findings support the implementation of such

interventions as part of comprehensive care for this patient population. However, it is important to acknowledge that not all patients are able to adhere to structured exercise programs, due to factors such as individual circumstances, disease severity, or comorbid conditions [36,38–40,46,48,49].

In this review, several studies reported improvements in symptom scores among MG patients who engaged in PA [37,39,42,43,45–47], consistent with previous research [19,50,51]. The mechanisms underlying these improvements may include enhanced muscle mass and strength through the mitigation of sarcopenia, as well as improved neuromuscular junction function, with collectively contribute to increased muscular capacity in patients with neuromuscular disorders [52]. Nevertheless, these findings should be interpreted with caution, as they contrast with other reports suggesting that MG symptoms may improve with rest and with and worsen with PA [22,39]. Importantly, one study [22] was a case series including only three patients, which substantially limits its methodological robustness and the generalizability of its conclusions. In addition, another study [39] reported adverse events associated with PA, including bulbar symptoms, increased fatigue, and one withdrawal potentially related to the training intervention.

In MG patients, quality of life is often significantly compromised. This has been previously reported in a study [53] that found elevated MG-QOL15 scores and a strong correlation between quality of life and perceived fatigue. However, in the present review, several studies [30,34,39,40,42,49] demonstrated that both PA and respiratory training led to improvements in quality of life among MG patients. Similar findings were reported in a study [54] involving patients with Guillain-Barré syndrome, where supervised exercise programs were associated with greater improvements in quality of life and reductions in fatigue compared to unsupervised training.

Performance in ADL also appears to benefit from PA interventions [30,34,38,40]. This is consistent with findings from a previous study [55] involving patients with inherited neuromuscular disorders such as limb-girdle muscular dystrophy and Charcot-Marie-Tooth disease, which showed that insufficient PA was associated with significantly lower ADL functionality (odds ratio: 4.1; 95% CI: 1.1-15.6) [55]. However, not all studies have reported significant improvements. A pilot study [56] found no statistically significant differences in ADL performance following an exercise intervention. This may be attributed to the study's primary focus on fatigue reduction, with ADL performance assessed as a secondary outcome, potentially limiting the power to detect changes in this domain [56].

Given that MG is characterized by muscle weakness, the improvements in symptoms observed following PA and respiratory training may be explained by increased muscle strength in both unaffected and affected muscle groups [19]. This gain in strength was reported in several studies included in this review [31,35]. However, one observational study [31] did not find a significant correlation between strength and symptom improvement. This discrepancy may be due to the non-randomized design, which limits the ability to control and tailor exercise interventions. In contrast, the RCT by Deliana T, et al. [35] implemented a structured and supervised training protocol, which may have contributed to the more favorable outcomes observed.

Sarcopenia is a common problem in MG [19]. Prior studies have reported associations between sarcopenia in MG and reduced engagement in PA and respiratory training [19,57,58], movement limitations due to impaired neuromuscular transmission [57,58], and prolonged glucocorticoid exposure [19]. These factors may lead to physical deconditioning [19,57,58]; therefore,

PA is recommended in several publications [30–32,36,39,40,43], consistent with the findings of the present review. Moreover, this deconditioning appears to be reversible through the implementation of structured PA and respiratory training programs [18,42].

Consistent with findings from a previous review [51], aerobic capacity is often reduced in patients with MG. In the present review, several studies demonstrated that aerobic PA led to improvements in this parameter [30–32,36,39,40,43]. Similar outcomes have been reported in research involving patients with other neuromuscular disorders [59,60], where short-term increases in aerobic capacity were observed following tailored exercise programs designed for these conditions.

Regarding pulmonary function, a prior review [61] evaluated the effects of respiratory muscle training and, in contrast to the findings of the present review [42–48], did not report significant improvements in lung function variables such as FVC or FEV1. This discrepancy may be explained by the broader scope of that review [61], which included multiple neuromuscular diseases and only one MG-specific study in its quantitative synthesis, potentially limiting its relevance to the MG population.

In terms of efficacy and safety, all types of exercise programs included in this review yielded positive outcomes for patients with MG [30–49]. However, to ensure that PA is beneficial and well-tolerated, specific exercise prescriptions should be followed. For aerobic activity, approximately 150 minutes per week of light to moderate intensity may be considered where tolerated. For resistance training, loads around 60-80% of the one-repetition maximum may be used to achieve benefits [19]; however, this range should be viewed as illustrative and titrated conservatively to symptoms, disease stability, and

clinical judgment. In the case of respiratory muscle training, training parameters should be interpreted according to the specific modality used. For pressure-threshold inspiratory muscle training, initial loads around 30% of PImax, with progression toward 50-60% as tolerated, have been reported in some studies [44,48]. However, these parameters were derived from small samples and should not be generalized to the full spectrum of patients with MG. Respiratory muscle training should be initiated only in clinically stable patients and individualized according to baseline respiratory function and overall clinical status [48]. In patients with markedly reduced inspiratory muscle strength, pressure-threshold loading may be contraindicated or should be undertaken only with extreme caution and close specialist supervision due to the risk of inspiratory muscle fatigue and respiratory deterioration [62,63].

4.1. Limitations and strengths

This review presents several limitations. First, the included studies employed heterogeneous interventions, as not all applied the same type of training program for patients with MG [35–38,40,48,49]. Additionally, only seven studies were RCT, while the remaining studies consisted of non-randomized trials [44,46], quasi-experimental designs [39,45,47], and observational studies [30–34,41–43]. Several of our meta-analyses exhibited substantial between-study heterogeneity. Beyond heterogeneity of interventions and designs, additional limitations warrant caution. Many included studies had small sample sizes [39,45,47] and short follow-up [35–39,45,46], and blinding was often unclear [36–38,42,45,47]. We also observed indications of publication bias in several funnel plots, which may limit the generalizability of the pooled estimates.

Despite these limitations, the review has notable strengths. A total of 20 studies were included in the qualitative synthesis [30–49], and 10 studies contributed to the quantitative synthesis [30,34,38–40,42–44,46,47]. Across studies, 1,366 participants with mild to moderate MG were analyzed; clinical characteristics and interventions varied across trials, which strengthens the reliability of the findings. Furthermore, many studies demonstrated a low risk of bias [31,32,34,36,38,41–43,45–49], while only seven studies were rated as having moderate risk of bias [30,33,35,37,39,40,44].

4.2. Implications for clinical practice

The implementation of PA and respiratory training may offer significant benefits for patients with mild to moderate MG, including improvements in symptoms, quality of life, physical function, and respiratory capacity [30–49]. Given the limited number of high-quality RCT and the heterogeneity of interventions, these observations should be interpreted cautiously. Awareness of these benefits may enable healthcare professionals to confidently recommend PA as part of a comprehensive treatment plan. However, the successful implementation of exercise interventions requires oversight by a multidisciplinary healthcare team to ensure that the training program is appropriately tailored to the patient's condition and to prevent disease exacerbations [64].

In addition to MG-related symptoms, the main barriers to adherence identified in this review were comorbidities and lack of time [36,38–40,46,48,49]. Therefore, it is essential that the multidisciplinary team provides personalized exercise recommendations that are both safe and feasible, taking into account each patient’s individual characteristics and circumstances [65].

5. Conclusion

In conclusion, the qualitative synthesis and meta-analyses conducted in this review suggest that PA and respiratory muscle training may provide benefits for patients with mild to moderate MG, including improvements in symptom severity, performance in ADL, quality of life, physical fitness, and respiratory function. These findings should be interpreted cautiously, as several limitations could affect the certainty of the evidence—notably indications of publication bias and heterogeneity in several meta-analyses. Based on these findings, healthcare professionals may consider implementing PA and respiratory training as part of the therapeutic approach for this patient population. However, the individual clinical status and personal characteristics of each patient with MG must be carefully evaluated, as these factors can pose challenges to the application of such interventions. Therefore, it is essential that a multidisciplinary care team assess each case individually to design and supervise personalized training programs that are both safe and effective.

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Data Availability Statement

All data that supports the findings of this review are available within the article itself and its supplementary data.

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Competing Interests Statement

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Author Contributions

Conceptualization: GGV, VSF, JALA. Formal analysis: VSF, VMP, RMMM. Funding adquisition: VMP, RMMM, CMB. Investigation: GGV, VSF, JMCT. Methodology: GGV, VSF, RMMM, CMB. Project administration: JALA, JMCT. Resources: VSF, VMP, JMCT. Software: VSF. Data curation: JMCT. Supervision: JALA. Validation: GGV, VSF, VMP, RMMM, CMB, JALA, JMCT. Visualization: VMP, RMMM, CMB. Writing – original draft: GGV, VSF, JALA. Writing – review and editing: GGV, VSF, VMP, RMMM, CMB, JALA, JMCT.